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Review

FMRP and CYFIP1 at the synapse and their role in psychiatric vulnerability

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Short Title: Synaptic FMRP & CYFIP1 and psychiatric disorders

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28 **Abstract**

29 There is increasing awareness of the role genetic risk variants have in mediating vulnerability to psychiatric
30 disorders such as schizophrenia and autism. Many of these risk variants encode synaptic proteins, influencing
31 biological pathways of the postsynaptic density and, ultimately, synaptic plasticity. Fragile X Mental Retardation 1
32 (*FMR1*) and Cytoplasmic FMRP-Interacting Protein (*CYFIP1*) contain two such examples of highly penetrant risk
33 variants and encode synaptic proteins with shared functional significance. In this Review, we will discuss the
34 biological actions of FMRP and CYFIP1, including their regulation of *i*) protein synthesis and specifically FMRP
35 targets, *ii*) dendritic and spine morphology and *iii*) forms of synaptic plasticity such as long-term depression. We
36 draw upon a range of preclinical studies that have used genetic dosage models of *FMR1* and *CYFIP1* to determine
37 their biological function. In parallel, we discuss how clinical studies of Fragile X Syndrome or 15q11.2 deletion
38 patients have informed our understanding of FMRP and CYFIP1 proteins, and highlight the latest psychiatric
39 genomic findings that continue to implicate FMRP and CYFIP1. Lastly, we assess the current limitations in our
40 understanding of FMRP and CYFIP1 biology and how they must be addressed before mechanism-led therapeutic
41 strategies can be developed for psychiatric disorders.

42

43 **1. The synapse and postsynaptic density proteins**

44 Neurotransmission between presynaptic and postsynaptic terminals is the adaptive communication mechanism
45 linking neurons and other cell types into neural circuits and networks, which form the basis of synaptic plasticity,
46 cognition and behaviour (1,2). The majority of excitatory, glutamatergic synapses in the mammalian brain are
47 located at small dendritic protrusions, or spines (3), and contain a prominent assembly of proteins at the
48 postsynaptic membrane known as the postsynaptic density (PSD) (4,5). Proteomic profiling of the PSD has
49 revealed over 1000 different proteins (6–8), many of which converge on the regulation of synaptic plasticity
50 through biological pathways controlling protein synthesis, receptor trafficking or structural rearrangements (9–
51 11).

52 **2. Synaptic FMRP: regulator of mRNA and local translation**

53 One such synaptic protein is Fragile-X Mental Retardation Protein (FMRP), encoded by the *FMR1* gene
 54 (Xq27.3)(12) and the monogenic cause of neurodevelopmental disorder Fragile X Syndrome (FXS) (13). *FMR1*
 55 mRNA is expressed in the neuronal cell body, developing and mature axons, dendrites and dendritic spines, as
 56 well as the nucleus (14,15), but not across all neuronal populations (16,17). FMRP is a RNA binding protein (RBP)
 57 with multiple structural motifs for binding RNA (such as KH domain and RGG box) (18), capable of regulating the
 58 dendritic sequestering, and localisation, of hundreds of target neuronal mRNAs (19,20), either through direct
 59 interactions or via intermediary interactions with noncoding RNA (21,22).

60 FMRP, its target mRNA and other protein partners, together form large messenger ribonucleoparticles (mRNPs)
 61 (23). Within the mRNP, FMRP plays a key role in the translational silencing of its target mRNA (24–27), required
 62 during the transport of mRNA along dendrites (28), before synaptic activation results in the docking of the
 63 mRNPs to the spines and subsequent translation (29,30). FMRP specifically regulates the rate-limiting step of cap-
 64 dependent mRNA translation *initiation* by binding to the initiation factor eIF4E and FMRP-binding partner CYFIP1
 65 (see **Section 4** later) (31,32), although initiation may also be regulated via FMRP ubiquitination or sumoylation
 66 (33–35). FMRP also controls *elongation* stages of mRNA translation by stalling ribosomes on FMRP target
 67 transcripts (19,24), although how FMRP switches between the regulation of initiation and elongation is currently
 68 unknown (36). FMRP is therefore a critical mediator of local translation of mRNA targets, acting at both
 69 presynaptic and postsynaptic terminals (24,37,38). Some of the key biological roles of FMRP at postsynaptic
 70 terminals are highlighted in **Figure 1**.

71 Beyond translational silencing, FMRP plays other biological roles (39) including RNA editing (40), the regulation of
 72 mRNA target stability (41), and ion-channel binding (42,43), collectively influencing calcium signalling (44),
 73 activity-dependent neurodevelopment (45) and the balance of excitatory/inhibitory circuits (46,47). The
 74 additional functions of FMRP might explain instances where FMRP does not appear to be a straightforward
 75 repressor of protein synthesis (48), perhaps most pertinently through FMRP's ability to influence the stability of a
 76 subset of mRNAs (22,49).

77 **3. FMRP targets**

78 Considerable effort has been made to identify the mRNAs targeted by FMRP so that biological pathways affected
79 by mutations in *FMR1* can be better predicted. Such studies have used immunoprecipitation followed by either
80 microarray (50,51) or high-throughput sequencing (19,52) to determine FMRP-bound mRNAs. Due to varied
81 methodology and tissues (as well as influence from type I and II errors), these lists of FMRP targets differ
82 considerably (52,53). Therefore, precisely which mRNAs are bound by FMRP is uncertain and likely to be
83 somewhat tissue-specific. Two studies using mouse cortical tissue and comparable methodology (high-throughput
84 sequencing of RNA isolated by crosslinking immunoprecipitation) yielded highly overlapping results: 89% of
85 mRNAs identified as FMRP targets by Darnell and colleagues (19) were also identified by Maurin *et al* (52). Still,
86 only a small subset of the proposed targets have been validated (23,49,54–57).

87 Gene ontology analyses of brain-derived FMRP targets confirm an overrepresentation of genes involved in
88 functions related to synaptic activity, plasticity, development and anatomy (19,52,58), consistent with studies of
89 FMRP function. The proteins they encode include both presynaptic and postsynaptic components. Of these are
90 subunits and interactors of receptor complexes considered central to synaptic plasticity phenotypes associated
91 with FXS, chiefly the mGluR5 and NMDA receptor signalling complexes (19). The observation that FMRP binds
92 some presynaptic proteins supports evidence that FMRP regulates protein synthesis during axon development
93 and synapse formation (59–62).

94 Whilst studies of FMRP targets have identified probable interactions between FMRP and ribosomal mRNAs,
95 further work is needed to determine whether the translation of these mRNAs are indeed repressed by FMRP
96 within the regulatory complex together with CYFIP1 and eIF4E proteins in the cell (31,32).

97 **4. Synaptic CYFIP1: a negative regulator of protein synthesis and cytoskeletal dynamics**

98 Cytoplasmic FMRP-Interacting Protein (CYFIP1) is a highly dynamic synaptic protein involved in numerous
99 biological pathways through an array of protein-protein interactions (**Figure 1**) (63). Originally known as a
100 Specifically Rac1 Activated protein 1 (SRA-1)(64), CYFIP1 was later found to bind with FMRP (12,65), forming a
101 critical CYFIP1-FMRP complex at the synapse (31). Specifically, FMRP-bound CYFIP1 acts as a non-canonical eIF4E-
102 binding protein (4E-BP) (31), thereby providing competition for the binding of eIF4E to the translation initiation

103 complex (eIF4E-eIF4G) (66,67). Overall, it is this eIF4E-CYFIP1-FMRP complex, together with its target mRNA, that
104 represses translation at dendritic and synaptic sites (31). Upon synaptic activation via Tropomyosin receptor
105 kinase B (TrkB) or group I mGluRs, eIF4E is released from CYFIP1-FMRP, and permits the translation of target
106 mRNAs (31). A subsequent study has implicated a MAP-kinase-interacting kinase (MNK)-dependent pathway in
107 the release of the inhibitory CYFIP1-FMRP complex from target mRNA, via MNK phosphorylation of CYFIP1
108 protein, in the early phase of LTP, thereby permitting translation (68).

109 Aside from its role in regulating protein synthesis, CYFIP1 forms part of the ~400kDa heteropentameric WAVE
110 regulatory complex, which also contains WAVE1/2/3, ABI1/2, NCKAP1 and HPSC300 components (69). Without
111 CYFIP1, the WAVE complex promotes actin cytoskeleton remodelling via the Arp2/3 complex (70–72), impacting
112 on aspects of dendritic spine formation, stability, morphology, migration and excitability (73). The role of CYFIP1
113 is to maintain the WAVE complex in an inhibited state, until the GTPase, Rac1, causes the dissociation of CYFIP1
114 from the WRC and allows actin remodelling to proceed via Arp2/3 (74).

115 CYFIP1 belongs to the two aforementioned complexes, FMRP and WAVE, in a mutually exclusive manner, skewed
116 towards greater association with the WAVE complex, under basal conditions (74). Notably, synaptic activation
117 changes the protein conformation of CYFIP1, from globular to planar, and drives the distribution of CYFIP1 protein
118 further towards the RAC1-WAVE complex, with a concomitant decrease in the eIF4E-CYFIP1 complex (71,74,75).
119 Therefore, CYFIP1 is a central molecular mediator that bridges the two processes of mRNA translation and actin
120 dynamics, both essential for synaptic plasticity (76–78). Other molecular roles for CYFIP1 are being explored,
121 including its role presynaptically. For instance, presynaptic function is altered in the hippocampus of juvenile
122 *Cyfp1* KO mice, thought to derive from changes in presynaptic terminal size and enhanced vesicle release
123 probability, and driven by dysregulation of the WAVE complex (79). These findings closely align with previous
124 findings in *cyfp1* mutant fly models that specifically found alterations in actin polymerisation in presynaptic
125 terminals. (65,80). More recently, *Cyfp1* KO mice were found to have decreased myelination of callosal axons,
126 alongside impaired presynaptic neurotransmission in the corpus callosum (81).

127 CYFIP1 has a closely related paralogue, CYFIP2, with over 88% amino acid identity (12). Like CYFIP1, CYFIP2 is
128 found at excitatory (82) and inhibitory (83) synapses, and binds both to the WAVE complex (63,69) and to FMRP

129 (12). Interestingly, CYFIP2 additionally binds to FMRP-related proteins, FXR1P and FXR2P, while *CYFIP2* mRNA is a
130 target of FMRP (19), implying a further layer of feedback between FMRP and the family of CYFIP proteins.
131 However, the molecular redundancy between these paralogues is limited, given that the deletion of both copies
132 of *CYFIP1* is embryonically lethal (74,84). Furthermore, CYFIP1, but not CYFIP2, has been consistently associated
133 with neuropsychiatric disorders (82,83), although see (85).

134 **5. Psychiatric disorders and the synapse**

135 Considerable evidence suggests that a wide range of neuropsychiatric disorders such as FXS, Autism Spectrum
136 Disorders (ASDs), schizophrenia, intellectual disabilities (ID), and bipolar disorder exhibit convergent synaptic
137 pathology (6,32,86–91). Synaptic dysfunction has been observed at several levels including: genetic alterations
138 (92–94); aberrant proteins (95) and their translation (25,96–98); molecular signalling pathways (99–101); spine
139 morphology (102); aberrant synaptic plasticity (103–105); neurocircuitry and connectivity (106). These
140 interrelated observations highlight impaired synaptic function as a common feature of several neuropsychiatric
141 disorders (91,94,107).

142 In light of this view, and the biological importance of FMRP and CYFIP1 at the synapse (outlined in **Sections 2 and**
143 **4**), we will now consider the role of FMRP and CYFIP1 in the aetiology of psychiatric disorders, using data from
144 human patient studies, especially psychiatric genomics, and preclinical models.

145 **6. FMRP and FMRP targets in psychiatric disorders**

147 ***6.1 FXS patients and *Fmr1* knockout models***

148 In humans, the transcriptional silencing of the *FMR1* gene by a triplet repeat expansion (beyond 200 repeats,
149 typically ~800) in the 5'- untranslated region of *FMR1* (108) leads to FXS (13,109). FXS patients display a broad
150 range of abnormalities including increased immaturity of dendritic spines (110–112); altered molecular signalling
151 (23); increased levels of basal protein synthesis (113,114); altered neuron and circuit excitability (115); structural
152 and connectivity defects in brain networks (116); and a range of cognitive and behavioural phenotypes that
153 overlap considerably with intellectual disability and ASD (117–119). Indeed, FXS represents the single most
154 common form of inherited ID with a prevalence of 1:4,000 males and 1:8,000 females (120) and the most

common, single-gene cause of ASD (108,117). FMRP may also be involved in other neuropsychiatric disorders, beyond FXS and related ASDs, including schizophrenia and bipolar disorder (121–125).

The effects of *Fmr1* mutations have been interrogated preclinically for 25 years through the *Fmr1* knockout (KO) mouse model (126), and with the advent of modern gene-targeting technologies, the *Fmr1* KO rat model (127,128). Many of the features of human FXS have been recapitulated in *Fmr1* KO mouse and rat models, especially in three key areas: dendritic spine maturation (112,127,129,130); elevated basal protein synthesis (127,131–133); and behavioural/cognitive phenotypes, including ASD-like abnormalities (134), abnormalities in social interaction and interest (135), social anxiety (136) and reduced behavioural flexibility/reversal learning in a variety of tasks (127,137–141).

In addition to heightened global protein synthesis, *Fmr1* KO rodents display a lack of metabotropic glutamate receptor (mGluR)-dependent translational control, which results in an elevated protein synthesis-dependent form of synaptic plasticity, known as metabotropic glutamate receptor (mGluR)-mediated long-term depression (127,142–145). Increased mGluR-dependent translation is thought to occur through excessive activation of the mGluR5 subtype, given that reductions in mGluR5 expression (132), or the mGluR5 antagonist MPEP (46,146), can rescue several *Fmr1* KO phenotypes. The altered mGluR5 signalling in the absence of *Fmr1* appears to be mediated through the preferential interaction of mGluR5 with activity-dependent isoforms of Homer1 over constitutive Homer proteins (147,148).

The deletion of *Fmr1* results in the loss of the repressive eIF4E-Cyfp1-FMRP complex, which de-represses the initiation complex, eIF4F, required for cap-dependent translation initiation of FMRP targets (149). It was shown that an inhibitor of the eIF4F complex, which creates free eIF4E, increases the abundance of the eIF4E-CYFIP1-FMRP complex (with a parallel decrease in the CYFIP1-WAVE complex) in *Fmr1* KO mice, and the restoration of this imbalance rescues spine and memory deficits in these animals (150). Hence, studies of the *Fmr1* KO rodent model have illuminated a variety of molecular mechanisms relevant to FXS, especially those pertinent to the regulation of protein synthesis, and may provide biological targets for therapeutic intervention (24), complementing ongoing clinical trials in human FXS patients (151,152).

180 6.2 FMRP and FMRP targets in psychiatric genomic studies

181 Beyond repeat expansions in the *FMR1* gene, a number of rare pathogenic point mutations have been reported
182 that cause developmental delay and intellectual disability reminiscent of FXS (153–157). Further evidence
183 suggests that mutations in the autosomal homolog *FXR2* gene might also contribute to intellectual disability (158–
184 160). Whilst variants affecting the related *FXR1* gene confer risk to schizophrenia, bipolar disorder and autism
185 (161–165), the genetic link between *FMR1* and psychiatric disorders derives from enrichment of association
186 within the gene targets of FMRP (among which the Fragile-X family genes themselves are included).

187 A set of FMRP target mRNAs derived from a study of mouse cortical polyribosomes (19) have been recurrently
188 highlighted in the literature due to their enrichment for genes associated with an array of psychiatric disorders.
189 Through large-scale genome-wide association studies, these 842 FMRP targets have been shown to be genetically
190 associated with schizophrenia (161,162), autism (166), major depressive disorder (167) and bipolar disorder (58).
191 In addition to the risk conferred from common variation, this gene set is enriched for rare variants from patients
192 with schizophrenia (168–171), autism (172) and bipolar disorder (173), *de novo* variants from patients with
193 schizophrenia (174) and autism (175–177), and to a lesser extent copy number variants from patients with
194 schizophrenia (178–180). The convergence of risk from multiple different types of genetic variant forms a strong
195 evidence base implicating this gene set in psychiatric pathology. Conversely, FMRP targets derived from a study of
196 human embryonic kidney cells (51) do not appear to be associated with psychiatric disorders (166,168),
197 highlighting the tissue specificity of these relationships.

198 Brain FMRP targets overlap considerably with other gene sets associated with psychiatric disorders, such as genes
199 encoding postsynaptic density proteins and those involved in calcium signalling, synaptic plasticity, learning and
200 memory (19,52,58,181). However, despite these overlaps, the enrichment of brain FMRP targets for association
201 with psychiatric disorders is independent (58,162,168) and proportional to the confidence of binding by FMRP
202 (58). Moreover, in many instances, it appears that FMRP targets capture subsets of these other gene sets in which
203 genetic association is concentrated (58). Hence, this set of genes locally regulated by FMRP during plasticity and
204 development at the synapse may represent a collection of biological pathways important for the manifestation of
205 a range of psychiatric disorders.

206 **7. CYFIP1 in psychiatric disorders**

207 ***7.1 15q11.2 copy number variants and Cyfip1 dosage models***

208 The proximal long arm of human chromosome 15 (15q11.2-13.3) is a region of numerous low copy repeats that
209 can lead to aberrant meiotic chromosomal rearrangements. These result in deletions or duplications of sections
210 of DNA, known as copy number variants (CNVs), and occur at any of five common breakpoints (BP1-BP5) on
211 chromosome 15 (182). Neurodevelopmental psychiatric disorders Prader-Willi syndrome (PWS) and Angelman
212 syndrome (AS) are caused by deletions of paternal or maternal origin, respectively, and occur as either large
213 deletions (type I, between BP1-BP3) or smaller deletions (type II, between BP2-BP3). Meanwhile, *CYFIP1* is
214 cytogenetically positioned in the non-imprinted 500kb region between BP1 and BP2 on chromosome 15 (15q11.2
215 interval), along with 3 additional genes: nonimprinted in Prader/Willi Angelman 1 (*NIPA1*) and 2 (*NIPA2*), and
216 tubulin gamma complex associated protein (*TUBGCP5*) (183). The 15q11.2 chromosomal region was first
217 implicated with neurodevelopmental psychiatric disorders through the observation that type I deleted PWS or AS
218 patients, who lack the 15q11.2 interval, had more severe behavioural phenotypes compared to type II deleted
219 patients, in which the 15q11.2 interval is intact (184,185). Later, patients were identified with deletions and
220 duplications between BP1 and BP2, which specifically flanked the 15q11.2 interval itself (182).

221 Deletions or duplications of 15q11.2 are present in 1 out of 100 people that present for genetic screening, whilst
222 incidence in the general population is likely to be nearer 1 in 500 people (186). The CNV causes patients to display
223 language/motor deficits or delays, behavioural problems, autism and seizures (187–189), with deletions the most
224 impactful on cognition (187) and referred to as Burnside-Butler syndrome (182,186). It was recently observed that
225 15q11.2 deletion patients have structural and functional changes in the brain that likely relate to the
226 accompanying cognitive phenotypes, including a smaller left fusiform gyrus and altered activation in the left
227 fusiform and the left angular gyri using fMRI (190). In subsequent diffusion tensor imaging (DTI) studies, 15q11.2
228 deletion carriers show increased fractional anisotropy (191), indicating alterations in the white matter
229 microstructure (192). In keeping with these findings, white matter changes in 15q11.2 deletion patients closely
230 mirror the phenotypes of FXS patients (193), suggesting a common pathogenic pathway derived from disruption
231 of CYFIP1-FMRP protein complexes. Although the 15q11.2 deletion is not fully penetrant, as a significant

232 proportion of the general population are healthy carriers with no overt phenotypes (194), it is likely that
233 subclinical cognitive phenotypes exist even in these ‘healthy’ carriers (195).

234 Among the genes located within the 15q11.2 locus, *CYFIP1* is widely regarded as the most likely to confer the
235 biological and behavioural phenotypes associated with 15q11.2 BP1-BP2 CNVs (84,191). This is due, in part, to its
236 known functional association with the FXS-relevant protein FMRP (see **Sections 2, 3, 4 & 6**) (31,74). Furthermore,
237 the expression of *CYFIP1* and components of the WAVE complex is disrupted in patients carrying 15q11.2
238 deletions (196); iPSCs derived from these patients exhibit cellular phenotypes mediated by the *CYFIP1*-WAVE
239 complex (197); and the knockdown of *CYFIP1*, specifically, in human progenitor cells alters cytoskeletal
240 remodelling (198). However, the biological roles of the three remaining genes within the 15q11.2 interval requires
241 further delineation, as, like *CYFIP1*, they are all CNS expressed and their expression is altered in patients with
242 15q11.2 CNVs (199).

243 Great strides have been made in understanding the consequences of altered *Cyfp1* dosage through a variety of *in*
244 *vitro* and *in vivo* rodent preclinical models. For instance, the heterozygous deletion of *Cyfp1* in mice results in
245 changes in dendritic and spine morphology (74,82), which are similarly observed in a forebrain-specific
246 conditional homozygous knockout model (83), whilst the over-expression of *Cyfp1* also impinges on dendrite and
247 spine morphology (82,200). Meanwhile, *Cyfp1* appears to affect protein synthesis under basal and activity-
248 dependent conditions. The knockdown of *Cyfp1* in cortical neurons *in vitro* increases the translation of FMRP
249 target *Arc* under basal conditions and also ablates the activity-dependent translation of *Arc*, using BDNF
250 treatment to mimic synaptic activation (74). Similar findings were reported *in vivo* using *Cyfp1* heterozygous KO
251 mice, whereby BDNF treatment was insufficient to release the *Cyfp1*-FMRP complex from eIF4E, preventing the
252 formation of the eIF4F complex, which subsequently prevented activity-dependent translation of *Arc* protein (68).

253 Measures of synaptic plasticity in preclinical models of altered *Cyfp1* dosage have revealed elevated levels of
254 mGluR-mediated long-term depression, which become disassociated from mRNA translation pathways (84) –
255 findings that are reminiscent of *Fmr1* KO rodent models (127,144). Over-expressing *Cyfp1* in CA1 hippocampal
256 neurons can lead to increased excitatory neurotransmission, and a concomitant decrease in GABAergic
257 neurotransmission at inhibitory synapses, shifting the overall excitation/inhibition balance towards excessive

excitation (83). The same study also showed that the conditional, homozygous knockout of *Cyfp1* in CA1 hippocampal neurons increased inhibitory GABAergic neurotransmission, along with increased expression of GABA receptors, suggesting a shift of excitation/inhibition balance towards greater inhibition (83). However, in the haploinsufficient *Cyfp1* mouse model, which better models the reduced dosage of *CYFIP1* in 15q11.2 deletion patients, GABAergic signalling remains unaltered in the hippocampal dentate gyrus (201).

Brain connectivity and white matter architecture appear to be especially sensitive to reduced *Cyfp1* dosage. In *Cyfp1* heterozygous KO mice, bilateral connectivity was shown to be reduced across multiple brain regions using resting-state functional magnetic resonance imaging (81). These alterations were likely due to changes in corpus callosal white matter architecture, measured by i) a decrease in fractional anisotropy using DTI and ii) altered levels of myelination and presynaptic function. Furthermore, many of the white matter phenotypes, including decreased fractional anisotropy, were mirrored in a comparable rat model of *Cyfp1* haploinsufficiency (202). However, it is currently unclear why fractional anisotropy might be decreased in rodent models of reduced *Cyfp1* dosage, but increased in 15q11.2 deletion patients. This will require further study and may alter our current perception of the effect of CNVs of the 15q11.2 interval.

In vivo models of altered *Cyfp1* dosage also offer the chance to thoroughly assess changes in behaviour and cognition; prominent features in 15q11.2 deletion (and duplication) patients. Bozdagi and colleagues were the first to behaviourally assess *Cyfp1* haploinsufficient mice, and found many aspects of spatial and fear learning and memory to be intact, with the exception of a rapid loss of extinction memory assessed using the inhibitory avoidance paradigm (84). Subsequent analysis of *Cyfp1* heterozygous KO mice and rats have shown specific deficits in motor learning (81,203), sensorimotor gating measured by prepulse inhibition (81) and behavioural flexibility (202). Meanwhile, the over-expression of *Cyfp1* results in cellular phenotypes, particularly at the dendritic level (200), but appears to have little effect on behaviour and cognition, with the exception of exaggerated fear responses (204). Overall, there is accumulating evidence that altering the dosage of *Cyfp1* in preclinical models leads to profound alterations in cellular and plasticity phenotypes, alongside mild behavioural phenotypes, many of which overlap with FXS and the *Fmr1* KO model (**Figure 2**), but also closely match the key clinical phenotypes of patients with chromosomal deletions (and duplications) of the *CYFIP1*-containing 15q11.2 interval.

285 7.2 *CYFIP1* variants in psychiatric genomic studies

286 Genomics studies in psychiatric populations have implicated the 15q11.2 BP1-BP2 deletion with a wide range of
287 psychiatric, neurodevelopmental disorders, including a 2- to 4-fold increased risk for schizophrenia (205,206); a
288 finding that has been replicated in many subsequent studies (92,179,207–210). Additionally, 15q11.2 deletions,
289 and duplications, predispose individuals to a five-fold risk of epilepsy (211), developmental and intellectual
290 disability (212–214), ADHD (215), major depression (216) and autism (187,217) (for further review, see (182,186)).
291 Meanwhile, common variants in *CYFIP1* have been reported to increase risk for ASD (218,219). Consistent with
292 the genetic findings, proteomic analysis of prefrontal cortex post-mortem tissue from schizophrenia patients
293 revealed altered levels of CYFIP1 and other proteins belonging to protein synthesis pathways (220).

294 The relevance of CYFIP1 to schizophrenia becomes especially apparent when considered in the wider context of
295 its biological actions within protein complexes. CYFIP1 is involved in the regulation of ARC protein and ARC-
296 related genes, sometimes referred to as the ‘ARC complex’ (a gene ontology-based complex). *CYFIP1* was first
297 associated with schizophrenia in studies that showed an enrichment of the ARC complex (containing 25 genes, of
298 which *CYFIP1* is one) in *de novo* CNV deletions from patients with schizophrenia (92). The genetic association of
299 this ARC complex with schizophrenia has subsequently been confirmed by exome sequencing studies that
300 assessed SNVs and indels (168,174) and larger studies of CNV deletions (178,179). Furthermore, the genetic
301 association with schizophrenia of FMRP targets (**Section 6.2**), which are regulated by the CYFIP1-FMRP complex,
302 lends additional evidence to the relevance of CYFIP1 to schizophrenia.

303 **8. Summary of findings and future directions**

304 FMRP and CYFIP1 are hubs for several biological pathways critical to synaptic plasticity. From preclinical models,
305 we know that reduced expression of either CYFIP1 or FMRP results in a set of core phenotypes: altered spine and
306 dendritic morphology, dysregulated protein synthesis and elevated long-term depression. A further layer of
307 complexity is added when it is considered that the concerted action of FMRP and CYFIP1, as part of the CYFIP-
308 FMRP complex, represses the translation of hundreds of FMRP targets, likely influencing multiple downstream
309 pathways. The importance of this system to synaptic function is recurrently highlighted by genetic studies

demonstrating the risk conferred to psychiatric disorders by variants affecting genes encoding CYFIP1, FMRP and their targets.

Nevertheless, there are many questions that still surround the biology of FMRP, CYFIP1 and FMRP targets in health and disease. For example, whilst FMRP synaptic biology is well-characterised and preclinical techniques can reverse disorder-relevant phenotypes (132,151), attempts to move these therapies into the clinic have been largely ineffective (152). This suggests that further mechanistic insights into the actions of FMRP are needed, alongside further refinement of therapeutic targets and/or strategies. Similarly, whilst FMRP targets are a disease-relevant group of mRNAs, their precise identity and biological function remains under-explored.

Meanwhile, the study of CYFIP1 has seen unprecedented advances in recent years, revealing an extensive array of synaptic roles, far beyond its initial characterisation as a binding partner to FMRP. Despite the rapid expansion of CYFIP1 studies, many fundamental questions remain and can be addressed in future studies, aided by advances in RNA sequencing, genetic-editing and proteomic technologies. Whilst extensively characterised, it is also worth noting that the behavioural phenotypes in models of *Fmr1* and *Cyfip1* deletion are only broadly similar, and in some cases diametrically opposed (221). These behavioural discrepancies could reflect the diversity of biological function, but might also derive from highly transient and localised interactions between these two proteins.

Penetrant risk variants affecting this biological pathway increase psychiatric vulnerability to a range of psychiatric disorders. For example, CNVs affecting *CYFIP1* predispose carriers to increased risk for schizophrenia (mainly 15q11.2 deletions), autism and intellectual disability (mainly 15q11.2 duplications), and likewise *FMR1* deletions predispose carriers to autism and intellectual disability. These apparently pleiotropic effects might suggest that the categorical nature of diagnoses for psychiatric disorders needs to be fundamentally re-evaluated. Indeed, at the clinic, there are many common patient symptoms that span across diagnostic categories, and patients often present with comorbidities. The genomic findings point towards a continuum of causality, whereby common biological mechanisms, influenced by a range of convergent genetic factors, span across the traditional diagnostic boundaries of psychiatric disorders. The highly tractable mechanism of CYFIP1-FMRP and the regulation of ARC, is one such biological pathway, offering a unique entry point for continued study and phenotypic rescue. The future development of novel, mechanism-based therapeutic approaches will be vital to meet the ever-growing need to treat these common, yet debilitating, psychiatric disorders.

337

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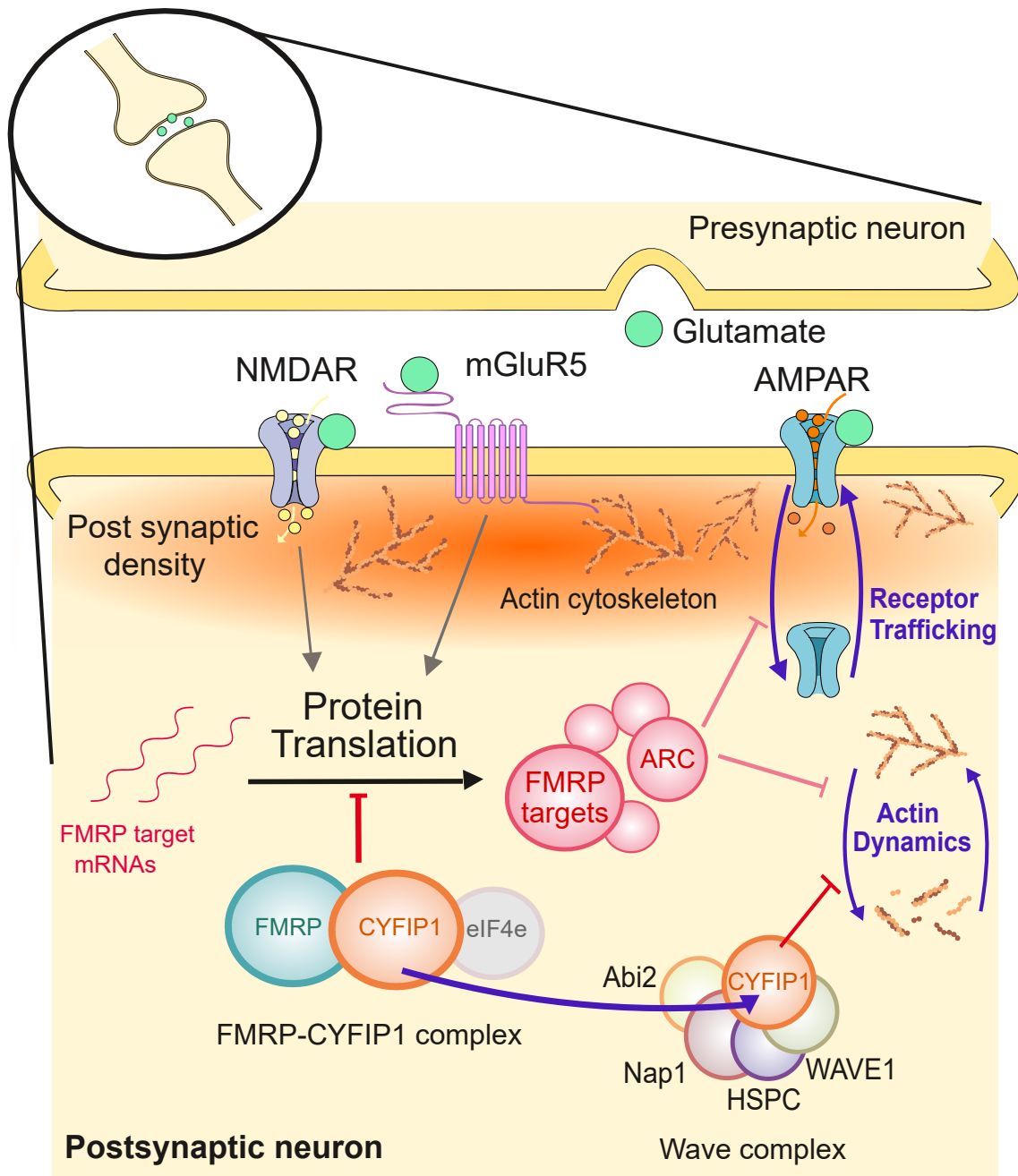
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Figure Legends

Figure 1: The biological roles of synaptic FMRP and CYFIP1 proteins in postsynaptic neurons. FMRP plays a key role in negatively regulating the translation of hundreds of FMRP targets, including ARC, by forming a complex with CYFIP1, alongside initiation factor, eIF4e. The control of mRNA translation, and its repression by the CYFIP1-FMRP complex, is partly mediated through activation of upstream NMDA and mGluR5 receptors. FMRP targets such as ARC can drive changes in synaptic plasticity through regulation of AMPA receptors trafficking/internalisation and increasing actin cytoskeleton stability. Meanwhile, CYFIP1 can bind and inhibit the

910 WAVE regulatory complex, thereby blocking the promotion of actin cytoskeleton rearrangements. Preclinical
911 evidence suggests that under conditions of synaptic activation, CYFIP1 redistributes between the two main
912 complexes, with greater association with the WAVE complex and a reciprocal decrease with the FMRP complex.

913 **Figure 2:** Core set of overlapping phenotypes from preclinical *Fmr1* and *Cyfig1* deletion models. Rodent models
914 of *Fmr1* deletion (*Fmr1*^{-y}, whereby the single X-linked copy of *Fmr1* is deleted in males) or heterozygous *Cyfig1*
915 deletion (*Cyfig1*^{+/-}) mirror clinical populations with Fragile X Syndrome and 15q11.2 CNV deletions, respectively.
916 Moreover, these two rodent models share a core set of functionally-related neurobiological phenotypes,
917 including i) altered spine and dendritic morphology, ii) dysregulated protein translation and iii) elevated long-term
918 depression. Further work is required to fully delineate the consequences of *Fmr1* and *Cyfig1* deletion, as well as
919 characterise the similarities.



Common *Cyfp1* and *Fmr1* deletion phenotypes

Clinic/
population: 15q11.2 deletion

Fragile X Syndrome 

Preclinical
models: *Cyfp1*^{+/-} KO rodents

Fmr1^{-/-} KO rodents 

Protein level:  



